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THE ROLE OF THE UROLOGIST IN CHEMOTHERAPY OF HORMONE REFRACTORY PROSTATE CANCER

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In This Issue

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TAXANES: AN OVERVIEW OF THE PHARMACOKINETICS AND PHARMACODYNAMICS

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ABSTRACT

Paclitaxel and docetaxel have emerged in the last two decades as effective antitumor agents in a variety of malignancies. Paclitaxel is a semisynthetic taxane isolated from bark of the Pacific yew tree. Docetaxel is a semisynthetic taxane derived from the needles of the European yew (*Taxus baccata*). These compounds bind to tubulin, leading to microtubule stabilization, mitotic arrest and, subsequently, cell death. Plasma clearance of paclitaxel exhibits nonlinear kinetics, which results in a disproportionate change in plasma concentration and area under the curve (AUC) with dose alterations. In contrast, docetaxel has a linear disposition over the dose ranges used clinically, so its concentration changes linearly with changes in the dosage. Premedicating with corticosteroids and histamine H_1 and H_2 receptor antagonists is advocated prior to paclitaxel administration; prior to docetaxel administration, premedication with corticosteroids is suggested. The taxanes are metabolized in the liver by the cytochrome P-450 enzymes and are eliminated in the bile. The known metabolites are either inactive or less potent than the parent compounds. The toxic effects associated with paclitaxel therapy are mainly neutropenia, peripheral neuropathy, and, rarely, cardiotoxicity. Docetaxel toxicity produces mainly myelosuppression and a cumulative dose fluid retention syndrome. Paclitaxel demonstrates sequence-dependent interactions with cisplatin, cyclophosphamide, and doxorubicin. Docetaxel has shown increased myelosuppression with preceding ifosfamide in a preliminary study. The future holds increasing indications for taxanes in newer combination regimens; consideration of their pharmacologic characteristics is an important aspect of designing and applying new taxane-based treatment regimens. UROLOGY 54 (Suppl 6A): 22–29, 1999. © 1999, Elsevier Science Inc.

Taxanes are a novel family of structurally related compounds that share a core ring structure called baccatin III (Figure 1). Although cephalomannine was not widely developed, paclitaxel and docetaxel—the active ingredients in taxol and taxotere—demonstrated a wide spectrum of preclinical activity in a variety of malignancies. Their use has gained clinical significance over the past two decades.

Paclitaxel is originally a natural product derived from the bark of the North American yew tree, *Taxus brevifola*. Wani *et al*[1] discovered the chemical structure of paclitaxel in 1962, but its mechanism of action was not described until 1979 by Schiff and associates.[2] Clinical studies using paclitaxel commenced in the mid-1980s. French researchers then produced semisynthetic derivatives of baccatin III, an extract from the needles of the European yew *Taxus baccata*, and modified it with a chemically synthesized side chain. Docetaxel emerged as a result of these efforts and entered clinical trials in 1990.[3]

The metabolism and pharmacokinetics of these analogs have an impact on dosage and toxicity profiles. The knowledge of the comparative pharmacology of paclitaxel and docetaxel is important for administration of these agents and when considering the potential of drug interactions. Review articles addressing the pharmacology of taxanes in detail have been previously published.[4–8] These reviews emphasize the pharmacokinetic and pharmacodynamic characteristics of the taxanes that influence their clinical use.

STRUCTURE AND MECHANISM OF ACTION

The taxane class of compounds (Figure 1) is composed of a taxane ring with a 4-member oxetan

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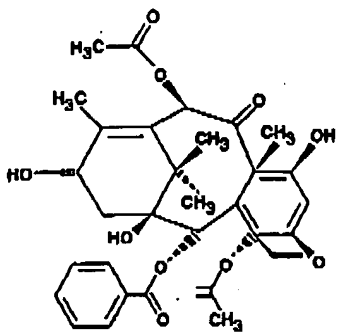

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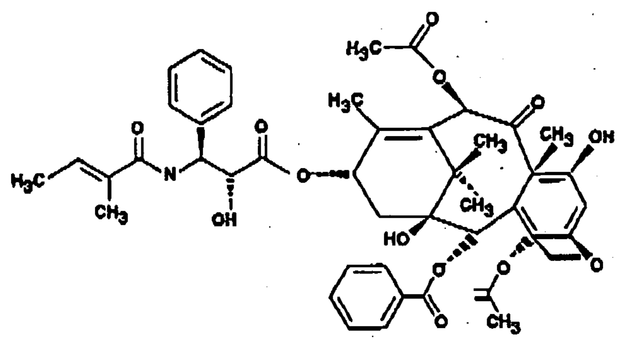

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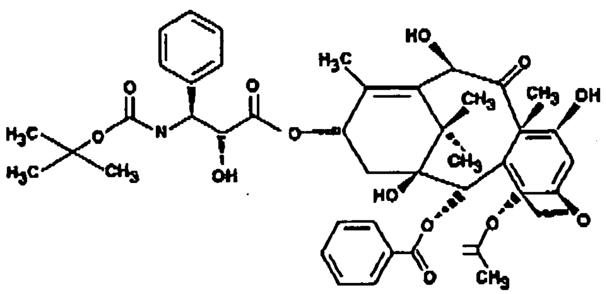

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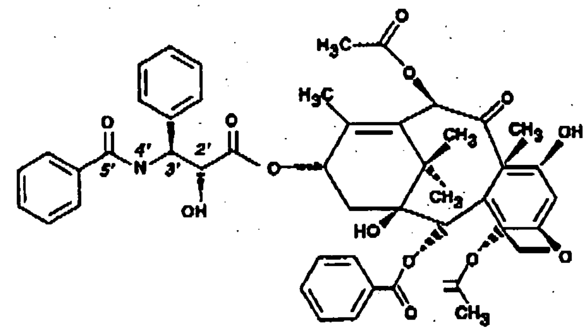


PACLITAXEL
NSC-125973

FIGURE 1. *The chemical structures of the basic taxane ring structure called baccatin III; paclitaxel, the natural product in taxol; docetaxel, a semisynthetic taxane in Taxotere; and cephalomannine. Also given are the NSC numbers for cross-referencing the structures to the chemicals repository at the US National Cancer Institute.*

ring attached at positions C-4 and C-5, and a bulky ester side chain at C-13.[1–4] The configuration of this ester chain is essential for the antitumor activity.[5] Docetaxel configuration differs structurally from paclitaxel in two ways: in the structure of the attachment to the C5′ carbonyl in the C-13 side chain; in the loss of the acetyl group esterified to the C-10 hydroxyl of the baccatin ring.[5,6]

The mechanism of action of taxoids is microtubule stabilization, which makes them resistant to disintegration and, hence, interferes with the normal mitotic process. Both taxoids bind to the β-subunit of tubulin, but the microtubules produced by docetaxel (average 13.4 tubulin subunits) are larger than those produced by paclitaxel (average 12 tubulin subunits).[7] The binding site for paclitaxel is distinct from that of colchicine, podophyllotoxins, or vinca alkaloids.[5] Docetaxel binds more avidly to tubulin and is retained longer intracellularly than paclitaxel. This may explain why docetaxel appears to be two to four times more potent than paclitaxel in studies of antitumor efficacy.[8]

The transition between microtubule stabilization and cell death affected by the taxanes is not clear. It is proposed that the taxanes lead to activation of apoptosis and subsequent cytotoxicity.[9] Studies in human myeloid leukemia cell lines corroborate this observation of paclitaxel-induced apoptosis involving phosphorylation pathways.[10] The induction and modulation of p53 have been demonstrated, but are not essential for the initiation of apoptosis. Bcl-2 overexpression was also found to delay paclitaxel-induced apoptosis.[11] Paclitaxel results in the direct phosphorylation of bcl-2, increased expression of bcl-x, and Raf-1, which causes a decrease of bcl-2. All of these mechanisms have been shown to increase apoptosis.[12–14] This indicates that paclitaxel has other mechanisms of action besides microtubule inhibition: These involve mainly bcl-2 phosphorylation, p53 modulation, and the apoptotic effect both linked to these and independent of them. The radiosensitization effect of paclitaxel has generated considerable interest.[14] Preliminary research also attributes immune modulation and anti-angiogenesis effects to taxanes.[15]

PHARMACOLOGY AND ADMINISTRATION

Paclitaxel

Taxoid compounds are insoluble in aqueous solution. Paclitaxel is formulated in 50% alcohol and 50% polyoxyethylated castor oil derivative. After

dilution into sodium chloride for injection, or 5% dextrose solution in *glass* containers, it is usually administered through specific in-line filters and tubing sets.[16]

The observation of hypersensitivity reactions to paclitaxel in early phase I trials led to prolonging the infusion time to either 6 or 24 hours. These reactions could be attributed to the taxoid itself or to the vehicle of formulation. Premedication with corticosteroids and H_1 and H_2 histamine receptor antagonists have been successful in reducing the incidence of severe reactions.[4–8]

Despite the fact that paclitaxel demonstrates greater antitumor activity when exposure is prolonged,[7,8] paclitaxel dosage has been gradually evolving toward shorter infusion times compared with initial phase I trials, where the dose-limiting toxicity was mainly neutropenia. In initial phase II studies, the dosage ranged from 135 to 250 mg/m^2, given as a 24-hour infusion with the use of premedication. As experience with paclitaxel increased in additional trials, shorter infusion schedules (1- or 3-hour) with the administration of premedication were accepted because of convenience. Safety was not compromised.[17,18]

In later trials, limiting the infusion duration to 3 hours, or even 1 hour, was studied.[4–8] Myalgia and neuropathy were the more significant adverse effects seen with short-term infusions; neutropenia and mucositis were more severe and more frequently observed with the prolonged administrations.[7] The incidence of hypersensitivity reactions did not differ significantly between brief versus prolonged duration of infusion if appropriate premedications were used.[19,20] The recommended dose of paclitaxel as a single agent or in combination now ranges from 135 to 250 mg/m^2, generally as a 3-hour infusion repeated every 3 weeks.

These adult dosages and treatment schedules cannot be directly extrapolated into the pediatric setting. On a given schedule, children tolerate higher doses better than adults do on a body surface area basis. For example, the recommended phase II dose of paclitaxel for a 24-hour infusion was 350 mg/m^2 for pediatric studies, which is significantly greater than the recommended phase II dose in adults of 250 mg/m^2. The underlying basis of this difference was not identified.[21] However, the average clearance rate in children at 290 mg/m^2 lies within the range reported for adults at 200–275 mg/m^2 (135 mL/min/m^2 in children versus 102 to 359 mL/min/m^2 in adults).[21] In addition, similar C_pMAX values of approximately 1 μmol/L were achieved in pediatric and adult patients by the end of 24-hour infusions.[5,21] These data do not identify the underlying reason for the pediatric difference, but do indicate that it cannot be a difference in the rate of drug elimination.

Docetaxel

Docetaxel is formulated in polysorbate 80 (Tween 80), and it can be administered after dilution in 5% dextrose solution or normal saline to a confirmed concentration of between 0.3 mg/mL and 0.9 mg/mL without in-line filters.[22] It was given without the use of premedication in its phase I trials with few hypersensitivity reactions observed. In phase II trials, these reactions were noted to occur more frequently and, hence, the use of premedication for docetaxel is recommended.[23]

Docetaxel was initially studied with doses ranging from 5 to 115 mg/m^2. It was administered in a variety of schedules with no premedication used. The maximum tolerated dose ranged from 80 to 115 mg/m^2, with neutropenia as the primary dose-limiting toxicity.[6,23] The recommended dose at present is 60–100 mg/m^2 as a 1-hour infusion every 3 weeks.

PHARMACOKINETICS

Paclitaxel

The taxanes are highly bound to plasma protein (paclitaxel 95% bound, docetaxel >90%[5]). Tissue distribution and binding influence the rate of plasma clearance; paclitaxel shows saturable distribution and nonlinear disposition.[6–8] An agent with nonlinear disposition lacks a proportional relationship between dose and the area under the plasma concentration of drug versus time curve, the so-called plasma AUC (Figure 2, curved line). This causes a disproportionate degree of change in AUC and in clearance of the drug, even with modest dose alteration. The mean clearance of paclitaxel appears to decrease as the dose is increased if the schedule remains constant. For a dose of 135 mg/m^2, the clearance rate is 14.7 L/hr/m^2; for a dose of 250 mg/m^2, the clearance rate is 8 L/hr/m^2. Hence, the severity and duration of toxicity increase disproportionately with dose escalation.[4]

This phenomenon has multiple clinical ramifications in the observed efficacy and adverse effects of the drug. The ramifications of saturable elimination have greater influence at higher doses where the plasma concentrations exceed the affinity constant for elimination (K_m). For 3-hour infusions, a 30% increase in dose from 135 mg/m^2 to 175 mg/m^2 increases the AUC by 80%, from 10.9 mmol/L · hr to 18.5 mmol/L · hr. Similarly, if the dose of paclitaxel is reduced because of excess toxicity from one cycle to another, then it decreases the AUC significantly and may compromise efficacy.

The comparison of response rates to dose intensity within or across clinical trials is very difficult if different dosing schedules of paclitaxel are used. For instance, consider two regimens of paclitaxel.

One regimen consists of 135 mg/m^2 as a 3-hour infusion, for 2 consecutive weeks, in a 4-week cycle; the other regimen consists of 250 mg/m^2 as a 3-hour infusion, repeated every 4 weeks. The dose intensity, using simple mathematics, is 67.5 mg/m^2/week for the first regimen described and 62.5 mg/m^2/week for the second regimen. The AUC for the regimen with the apparent lower dose intensity (62.5 mg/m^2/week) is 68% higher than the AUC achieved when the other regimen (67.5 mg/m^2/week) is followed.[4]

The nonlinear pharmacokinetics of paclitaxel could be attributed to its vehicle of formulation. Sparreboom and associates[24] demonstrated in a mouse model that when paclitaxel was formulated in 50% polyoxyethylated castor oil derivative, it had a nonlinear disposition; when formulated in Tween 80, the kinetics changed to a linear pattern. This provides an interesting theory, but translation of these results to human species is difficult because of the inherent differences in the metabolic pathways and their rate-limiting nature.

Docetaxel

In contrast to paclitaxel, the disposition of docetaxel is linear within the clinical dose range of 55 to 115 mg/m^2.[2-4] Therefore, the agent's AUC and clearance changes proportionately with dose alterations (Figure 2, straight line). In a pooled population study of adults, it was shown that plasma clearance of docetaxel fits a three-compartment model that gives a γ-phase half-life of 10 hours; this is similar to values ranging from 10–14 hours in individual studies.[5] Interestingly, docetaxel pharmacokinetics studied in a pediatric population of 23 patients using a 55 mg/m^2 dose demonstrated a biexponential disposition with elimination half-life of 2.4 hours and a clearance of 560 $mL/min/m^2$.[25] There are reports of age and body surface area affecting the clearance of docetaxel, but the clinical relevance of this effect is unclear and warrants further study.[5,6,14,23]

METABOLISM

Taxane metabolism is primarily hepatic and renal clearance is minimal (<5% excretion in urine).[25] Both taxanes are metabolized by hepatic cytochrome P450 enzyme systems and eliminated by biliary excretion.[5,26-29] Paclitaxel undergoes stereospecific CYP2C8 hydroxylation at the C6′ position of the taxane nucleus to form 6-α-hydroxy-paclitaxel, the major metabolite (Figure 3). Interestingly, this biotransformation is inhibited by 0.1% v/v Cremophor El.[29] Paclitaxel is also hydroxylated by CYP3A4 in the *para* position on the phenyl group attached to C3′ of the C-13 side chain to generate 3′-*p*-hydroxyphenyl-paclitaxel (Figure 3). Under in vitro conditions, the levels of each monohydroxylated species can be influenced by the inductive effects of comedications.[27] Each monohydroxylated species can be further metabolized, probably by the other pathway, to converge to the dihydroxy taxol metabolite, 6-α-hydroxyl-3′-*p*-hydroxyphenyl-paclitaxel.[28] The half-life of total metabolites (5.6 ± 0.4 hours) greatly exceeds that of unchanged taxol (2.9 ± 0.3 hours),[29] but hydroxylation significantly reduces potency in cytotoxicity assays, although not in microtubule binding assays.[5] Thus, although active, the metabolites have greater difficulty accessing the interior of target cells than paclitaxel.

Docetaxel is metabolized by successive oxidations on the *tert*-butyl group at the end of the C-13 side chain.[5] Enzymes of the CYP3A subfamily of cytochromes catalyze this reaction.[4,30] Like metabolites of paclitaxel, these docetaxel metabolites appear to be either inactive or much less potent than the parent compound.[5]

Given the fact that hepatic CYP450 metabolism is the major route of elimination of these drugs, one would expect changes in plasma clearance with changes in hepatic function. Administration of paclitaxel in patients with mild to moderate liver dysfunction (transaminases <10 times normal, and bilirubin 1.25 times normal) has been evaluated. A dose of 175 mg/m^2 is considered reasonably safe in this setting of patients less than 65 years of age with limited prior chemotherapy.[31] In analyses of patients with moderate hepatic impairment (aspartate transaminase [AST], alanine transaminase [ALT] > 1.5 times normal, and alkaline phosphatase > 2.5 times normal), a 27% decrease in clearance and a 38% increase in AUC of docetaxel were observed. The recommended dose for this patient population is 75 mg/m^2 over a 1-hour infusion.[23,32] The agent's safety has not been tested in patients with severe hepatic impairment.

Because of the hepatobiliary clearance of the taxanes, these have been the drugs of choice in patients with renal disease and in the elderly with impaired creatinine clearance. There is a report of safe and successful administration of paclitaxel in patients who have renal insufficiency (median creatinine of 2.25 mg/dL) with bladder carcinoma.[33]

TOXICITY

Myelosuppression is the dose limiting toxicity of both taxanes. Pharmacology studies during clinical trials of paclitaxel have found that the severity of neutropenia is most closely associated with the duration that plasma levels remain above 50–100 nmol/L.[34] Thus, the severity of the neutropenia is related to the infusion duration of paclitaxel; it increases with longer infusions. Mucositis follows

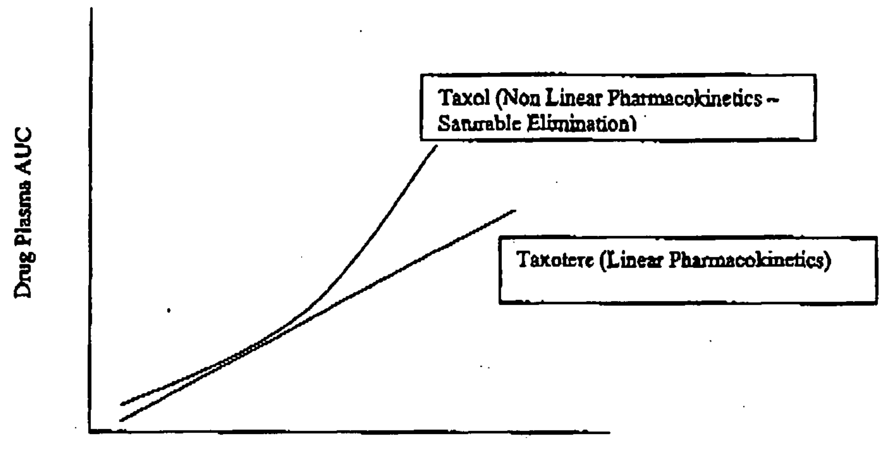
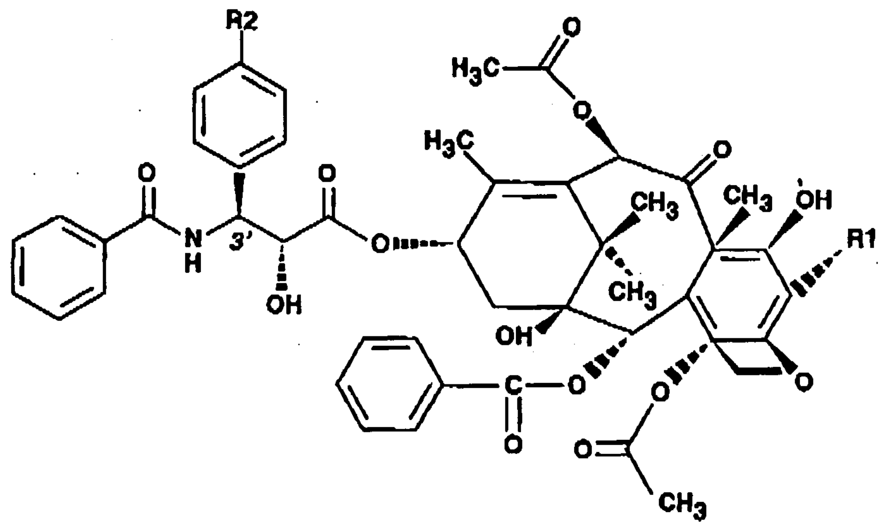


FIGURE 2. *A schematic showing the influence of dose on AUC following linear versus saturable nonlinear disposition.*



	R1	R2
Paclitaxel	H	H
M4	H	OH
M5	OH	H
Dihydroxy-Paclitaxel	OH	OH

FIGURE 3. *The chemical structures of the major hepatic metabolites of paclitaxel produced by the action of CYP450 enzymes. The M4 and M5 designation refer to the original nomenclature as published, and correspond to the C3'-para-hydrouphenyl- and the 6α-hydroxy- metabolites of paclitaxel discussed in the text.*

the same pattern.[5–8] Docetaxel causes neutropenia equivalent to that with a 24-hour infusion of paclitaxel.[7] Alopecia, mild gastrointestinal toxicity, and hypersensitivity reactions are observed with equal frequency during therapy with either taxane. Table 1 represents the comparative pharmacology and toxicities of paclitaxel and docetaxel.

Cardiac arrhythmias, especially asymptomatic bradycardias, are seen with paclitaxel.[4–8] The presence of a pacemaker or a prior history of cardiac conduction defects are relative contraindications to paclitaxel. Combinations with doxorubicin increase the incidence of congestive heart disease.[35] No adverse cardiac effects have been reported with docetaxel.[7]

TABLE I. *Comparative pharmacology of the taxanes*

Characteristic	Taxane: Paclitaxel	Taxane: Docetaxel
Dose	135–250 mg/m^2	60–100 mg/m^2
Infusion	3 hr	1-hr
Schedule	3-wk intervals	3-wk intervals
Premedication	Dexamethasone H_1 and H_2 antagonists just before treatment	Dexamethasone × 3 days
Pharmacokinetics	Nonlinear	Linear
Metabolism	Hepatic	Hepatic
Toxicity	Neutropenia Peripheral neuropathy Bradycardia	Neutropenia Fluid retention Dermatologic

Dose-related myalgia and neuropathy are seen with paclitaxel; particularly an increase in neurosensory symptoms are observed with cisplatin combinations.[34] Neurotoxicity is not prominent with docetaxel at the usual doses.[6,7]

Docetaxel demonstrates skin toxicity, including skin dryness and nail changes with thickening and discoloration, in some patients.[22,23] A cumulative fluid retention syndrome was observed in approximately 50%–60% of patients after three to five cycles of therapy, which may be totally dose related.[6,7] Clinical manifestations of weight gain, peripheral edema, pleural effusions, and ascites were noted. Premedication with corticosteroids for 3 days starting 1 day prior to docetaxel administration decreased the severity and incidence of fluid retention syndrome as shown in a prospective randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC).[36] Treatment discontinuation as a result of the syndrome was also significantly reduced (5% versus 32%, $P = 0.0032$). Hence, a 3-day course of steroid-based medication (8 mg dexamethasone, twice daily) is recommended.

DRUG INTERACTIONS

Cisplatin, when administered prior to paclitaxel, causes a significantly higher incidence of neutropenia as a result of a 25% reduction in paclitaxel clearance.[37] Reversing the sequence appears to eliminate this detrimental effect. The combination of carboplatin and paclitaxel has emerged as safe and well tolerated. The severity of thrombocytopenia is less than that seen with the administration of carboplatin alone.[38,39] These findings may reflect differential effects of the platinum compounds on CYP450 metabolism.[5]

One in vitro study on a human breast cancer cell line demonstrated a three-fold increase in cytotoxicity with administration of paclitaxel prior to doxorubicin.[40] However, this has not been clinically validated in vivo. Paclitaxel preceding doxorubicin is responsible for increased frequency of mucositis, cardiotoxicity, and neutropenia.[41] The pharmacokinetic studies indicate that there is decreased doxorubicin clearance; administering the drugs 24 hours apart may ameliorate this effect.[7,41] Alternating sequences of paclitaxel and cyclophosphamide revealed that cytopenias were profound when paclitaxel was infused first.[42] In vitro studies in human lung A549 and breast MCF-7 adenocarcinoma cells have shown that exposure to paclitaxel followed by melphalan, thiotepa, or cisplatin (alkylators) resulted in additive cytotoxicity.[43] A reverse exposure sequence, alkylator exposure followed by paclitaxel exposure, resulted in additive cytotoxicity in breast adenocarcinoma cells and an antagonist effect in lung cancer cells.[43]

Combinations of docetaxel with cisplatin or doxorubicin have not demonstrated any sequence-dependent alteration in toxicity.[31] An ongoing phase 1 study showed that dose-limiting toxicity occurred at lower doses of docetaxel and ifosfamide when ifosfamide preceded the taxoid.[44]

In vitro studies have been used to identify possible drug–drug interactions for the taxanes.[45] Treating patients on taxanes with CYP3A inhibitors, such as ketaconazole and erythromycin, is discouraged. Diphenhydramine, cimetidine, and ranitidine should not alter taxane pharmacokinetics, based on the fact that these drugs did not affect paclitaxel metabolism in vitro. Dexamethasone inhibited the formation of paclitaxel's metabolite at concentrations 15-fold higher than peak plasma levels in patients treated with premedication, so this is unlikely to have a clinical impact.[45] Docetaxel clearance and AUC were not affected by dexamethasone administration. Anticonvulsants, such as the barbiturates, appear to induce the metabolism of taxoids.[31] These drug interactions are a significant consideration in combination chemotherapy and in polypharmacy.[46]

CONCLUSION

The two important members of the taxoid family—paclitaxel and docetaxel—are similar in their mechanism of action and wide spectrum of activity. However, there are subtle differences in toxicity profiles. The manifestation of fluid retention syndrome appears to be unique to docetaxel, whereas cardiotoxicity is a side effect observed with paclitaxel alone. The pharmacokinetics of the two taxanes are distinct in the clinical dosage range. Paclitaxel shows a nonlinear disposition, which has a major impact on dose adjustments, severity of toxicity, and comparisons of efficacy between different schedules. Docetaxel demonstrates linear pharmacokinetics and has clearance and AUC proportional to dose. The taxanes are cleared by hepatobiliary excretion mediated by cytochrome P450 enzymes. Doses have to be adjusted for liver dysfunction, but they can be safely administered in moderate renal insufficiency.

There are no significant reported clinical interactions of taxoids with the premedications used to control hypersensitivity reactions. Sequence-dependent interactions with cisplatin, cyclophosphamide, doxorubicin, and ifosfamide are noteworthy because of their effects on toxicity and efficacy. Novel indications for the taxoids are constantly emerging, including use for peripheral stem cell mobilization.[47] New forms of taxoids are in evolution, including water-soluble agents, liposomes, and nanoparticles. The pharmacokinetics and pharmacodynamics of the taxoids currently in use, and those forthcoming, have multiple clinical and research implications. They also play an important role in the safe, successful, and efficacious use of these agents.

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